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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 06/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/858,200	MAKRIGIORGOS, GERASSIMOS M.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *14 and 15* is/are withdrawn from consideration.

5)☒ Claim(s) *12 and 13* is/are allowed.

6)☒ Claim(s) *1-11 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 4/12/04 has been entered.

2. This action is written in response to applicant's correspondence submitted 4/12/04. Claims 1 and 12 have been amended, and claim 16 has been added. Claims 1-16 are pending, claims 14-15 are withdrawn from prosecution. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The set of claims filed 4/24/04 are not in compliance with section 1.121 which requires that the text of ALL pending claims be included in the claim set. In the pending claim set, the text of claims 14 and 15 is not present. In the interest of proceeding with prosecution, the pending claims have been examined herein, but the next presented claim set should remedy this deficiency.

Priority

4. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-11 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, line 4, the phrase "the genomic genes" lacks proper antecedent basis in the claim because it is not clear which genes are "the genomic genes." Claims 2-11 are also indefinite over this recitation as they depend from claim 1.

In claim 3, the phrase "the whole gene" lacks proper antecedent basis in the claim as it is not clear which of the previously recited and required ten genes on the array or in the target is "the whole gene."

In claims 4 and 5 the phrase "the genes" lacks proper antecedent basis in the claims. It is confusing if "the genes" recited in claims 4 and 5 are the ten genes represented in the array or the ten genes required in the target DNA or both of these. Claim 1 does not require that the genes in the target and the genes on the array are the same, and thus the recitation in claims 4 and 5 is confusing.

In claim 6, the phrase "said at least 10 different genes" lacks proper antecedent basis because claim 1 recites two different groups of 10 different genes, one on the array and one in the target. Thus, it is confusing if "said 10 different genes" recited in 6 are the ten genes represented in the array or the ten genes required in the target DNA or both of these. Claim 1 does not require that the genes in the target and the genes on the array are the same, and thus the recitation in claim 6 is confusing. Claims 7-8 depend from claim 6 and are also indefinite over this recitation.

In claims 9 and 10 the phrase "said genes" lacks proper antecedent basis in the claims. It is confusing if "the genes" recited in claims 9 and 10 are the ten genes represented in the array or the ten genes required in the target DNA or both of these. Claim 1 does not require that the genes in the target and the genes on the array are the same, and thus the recitation in claims 9 and 10 is confusing.

Claim 16 is indefinite over the recitation "comprises at least 5 contiguous genes" because it is not clear if this means that a the target DNA sequence contains 5 genes that are each contiguous with respect to the genes themselves (i.e. intact) or if the claim intends that the 5 genes are contiguous within a genomic chromosome.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1, 2, 3, 4, 5, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Modrich et al. (US 5459039) in view of Chee et al. (Science, Vol. 274, pages 610-614, 25 October 1996), and optionally, further in view of Brown *et al.* (US 5376526).

Modrich et al. teach a method for identifying mutations in a target DNA sequence which comprises

(a) hybridizing the target DNA with a control DNA sequence to create a duplex, wherein the control DNA sequence is the wild-type DNA corresponding to the target DNA sequence (Col. 7, lines 6-8), and wherein said target DNA comprises a pool of nucleotide segments that collectively span at least 10 different genes (Col. 10, lines 18-21);

(b) tagging any mismatch in said duplex with a detectable moiety, wherein the detectable moiety is a protein (Col. 7, lines 8-10);

(d) removing the segments tagged with the detectable moiety (Col. 16, lines 15-18), and

(f) identifying the gene and gene segment the selected mismatch belongs to (Col. 16, lines 45-50).

Modrich *et al.* teach a method for detecting genetic mutations. Modrich *et al.* teach taht in the practice of this method the DNA molecules compared may comprise sequences encoding

up to the entire genome of an organism, including man, and thus, such a sample necessarily comprises a pool of nucleotide segments that span at least 10 different genes.

Modrich *et al.* do not teach steps in which the duplex is cleaved into segments of 50-300 bases or in which the tagged segments are contacted with a mutation scanning array. Thus, the method taught by Modrich et al. differs from the claimed method only in that the methodology used to identify the gene and gene segment to which the selected mismatch belongs is different.

Chee *et al.* teach a mutation scanning array that comprises a plurality of elements, wherein the elements contain immobilized oligonucleotides 8-50 bases long, that collectively span at least 10 different genes from the 5'to 3' end, wherein the genes can be either coding regions or the genomic genes, to identify mutations in a target sequence. Chee *et al.* teach the identification of mutations within segments of the human mitochondrial genome via hybridization to an array for the entire mitochondiral genome (p. 612), thus simultaneously analyzing the control region, 12 protein coding regions, 22 tRNA genes, and 2 ribosomal RNA genes (p. 613), and suggest that future arrays should query the entire human genome, an estimated 100,000 genes (p. 613). Further, Chee *et al.* a step in which molecules were fragmented to an average size of less than 100 nucleotides prior to hybridization, and that fragmentation improved uniformity and specificity of hybridization (p. 613, note 12).

With regard to claim 2, this claim encompasses methods in which DNA is amplified prior to the hybridizing step of (a), as the claim requires that the segments are amplified prior to being used on the mutation scanning array. Thus, the segments could be amplified and then tagged and be within the scope of this claim. Chee *et al.* teach methods which utilize amplified genomic

extracts (note 11) and methods in which labels are added to sequences prior to hybridization via PCR amplification (note 12).

With respect to claims 3, 4, and 5, Chee *et al.* teach that the array contains a set of probes representing every position across the mitochondrial genome, in which whole genes are represented by elements containing immobilized oligonucleotides that sample in 25-300 bases for the whole mRNA sequence of the represented gene, and further non-coding portions of the genes (such as promoters) would be represented as the entire mitochondrial genome is represented.

With regard to claim 11, the array used by Chee *et al.* is a microsphere.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used an array such as the one taught by Chee et al. for the identification of nucleic acid sequences containing mismatches identified by the method taught by Modrich *et al.* The ordinary practitioner would have been motivated by the teachings of Modrich et al. which provide that "any suitable analytical method (Col. 7, lines 40-42)" can be used to identify the fragments and by the teachings of Chee et al. who specifically provide nucleic acid arrays for the identification and localization of mutations in nucleic acid sequences. One would have been motivated to utilize the arrays taught by Chee *et al.* in order to take advantage of the benefits of microarray technology as taught by Chee *et al.*, for example, that compared to conventional techniques such as sequencing, with the use of array technology "sequence reading at the level of data analysis is automated: The sequences can be read in a matter of minutes" and that the microarray technology is "highly scalable" (p. 612). Thus, in

light of the teachings of Modrich et al. in view of Chee et al., the instant invention is prima facie obvious.

Optionally, further motivation to combine the teachings provided by Modrich *et al.* in view of Chee *et al.* is provided by the teachings of Brown *et al.* Brown *et al.* teach a method for genomic mismatch scanning which identifies mismatches throughout a genome and then identifies the gene and gene segment which contain the mismatch (Col. 3, lines 5-10). The method taught by Brown *et al.* is very similar to that taught by Modrich *et al.*, in that large regions of DNA are screened for mismatches. Brown *et al.* specifically teach that the isolated DNAs of their invention preferably are hybridized with "a partial or complete collection of cloned, amplified, or synthentic DNA sequences corresponding to known genetic locations, immobilized in an ordered array on a solid substrate such as a membrane or a silicon or plastic chip (Col. 8, lines 18-23)." Chee *et al.* provide such an array. Thus, in view of the teachings set forth by Modrich *et al.* in view of Chee *et al.* and further in view of Brown *et al.*, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have utilized the mutation scanning array taught by Chee *et al.* for identification of the mismatched sequences taught by Modrich *et al.*

9. Claims 6-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Modrich et al. in view of Chee et al., and optionally in view of Brown *et al.*, as applied to claims 1-5 and 11 above, and further in view of Cronin et al. (WO 98/30883).

The teachings of Modrich et al. in view of Chee et al., and optionally in view of Brown *et al.* are applied to the instant claim as they were to claims 1-4 and 11. Modrich et al. in view of

Chee et al., and optionally in view of Brown *et al.* do not teach methods in which the genes on the array are selected because of their association with particular diseases.

Cronin et al. provide methods for the detection of polymorphisms and mutations in genes (ABSTRACT). The particularly teach that mutations can be searched for in reference sequences that include genes to many different types of diseases and conditions, including cancer, diabetes, and tumor suppressor genes (pages 12-13). Thus, it would have been prima facie obvious to one of ordinary skill in the art to have included any or all of these types of genes on an array to be used in a mutation detection method such as the one provided by Modrich et al. in view of Chee et al., and optionally in view of Brown *et al.* The ordinary practitioner would have been motivated to utilize arrays containing the coding and non-coding regions of disease genes in the methods taught by Modrich et al. in view of Chee et al., and optionally in view of Brown *et al.* in order to have used such arrays in further methods for the detection of disease associated mutations.

Response to Remarks

The search has been updated and new rejections have been applied in view of references identified in the new search. While the previous rejections could have been maintained, the examiner believes that the newly applied references more directly address the claimed invention.

Nonetheless, applicant's remarks are addressed insofar as they might be related to the claimed invention.

Claims 12 and 13 are allowed in view of the terminal disclaimer. Claim 16 is rejected under 112 2nd paragraph but is free of the prior art. The claims are free of the prior art. The closest prior art, as cited in this office action, does not teach steps of treating to remove

spontaneous aldehydes, reacting with a repair glycosylase and then reacting with a compound of the formula X-Z-Y as recited in the instant claims. Therefore, the claims are free of the prior art.

Applicant argues at page 5 of the response that Modrich begins with a single known gene, rather than a population of multiple genes. This is no persuasive. Modrich *et al.* teach specifically teach that their method can be used to compare entire genomes, which certainly are comprised of hundreds of thousands of genes (Col. 10).

Applicants arguments in view of Wodicka in particular (page 7 of response) are moot in view of the newly applied Chee *et al.* reference. Chee *et al.* specifically teach an array for the identification nucleic acid fragments that have mutations.

Thus the claims remain rejected.

Applicant states at page 5 of the response that the invention is specifically directed to using a scanning array to scan at least ten different genes. However, it is first noted that this limitation is not within the claims. The claims require that array itself comprise probes to at least ten different genes, but the active process steps within the claims do not require a step wherein ten different genes are examined. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., scanning ten different genes) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). However, it is noted that it would be obvious to apply the method disclosed in the cited prior art to detect mutations in a multiplicity of genes, given that it was known in the art at the time the invention was made that mutations occur in many, many different genes in the human genome.

It is noted that the addition of such a limitation would require further search and examination by the examiner, to find and consider references which may be relevant to such a limitation.

Conclusion

10. Claims 12 and 13 are allowed.

11. Claim 16 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Gifford *et al.* (US5750335) teach a method for mismatch detection wherein mismatches are tagged with a mismatch binding protein and subjected to subsequent PCR amplification prior to identification of the mismatch (see for example Figure 4).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached by calling (571) 272-0782.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the

USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Juliet C. Switzer
Examiner
Art Unit 1634

June 17, 2004